THE EFFECT OF HYALURONIC ACID ON A RABBIT MODEL OF FULL THICKNESS ARTICULAR CARTILAGE REPAIR FOLLOWING ACUTE INJURY
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Introduction
Knee injuries are common in both the young and the athletic populations. While ligamentous and meniscal trauma constitute the majority of knee injuries, articular cartilage damage can and does occur frequently. Early detection of articular cartilage damage has dramatically improved with the advent of MRI, and focal defects as small as 1mm may now be detected(1). "Benign neglect" has been the treatment mainstay for small defects, although more aggressive treatments have included arthroscopic debridement alone or combined with drilling or microfracture of the involved area. Despite treatment, many articular lesions do progress, and ultimately the knee develops osteoarthritic changes. A variety of methods has been employed to enhance the repair of full-thickness cartilaginous defects, including transplantation of mesenchymal stem cells, perichondrial tissue, or isolated chondrocytes. These tissues have been transplanted alone and in resurfacings with biodegradable implants(2,3,4,5,6,7,8). Recent implantation of bone morphogenetic protein (BMP) absorbed on collagen was shown to improve the quality of the tissue in a repaired full thickness defect. While these techniques appear attractive, they are all invasive. A simple and cost effective medical therapy capable of augmenting the normal healing process would represent a significant advancement in the management of acute full thickness cartilage injuries. Over the past decade intra-articular injection of hyaluronate has been utilized in the management of osteoarthritis of the knee, and more recently has been shown to improve meniscal healing in an acute injury model (9). To examine the potential benefit of hyaluronate on articular cartilage repair, the effect of serial intra-articular hyaluronate injections on the healing of full thickness cartilage defects was explored utilizing a rabbit model.

Methods
Nineteen New Zealand white rabbits underwent bilateral knee arthrotomies. A 2mm full thickness articular cartilage defect was created on each medial femoral condyle and a full thickness scratch defect was created on each lateral condyle. Rabbits received serial intra-articular injections (0.5ml) of hyaluronic acid once a week for 3 weeks in the right knee, started at either one or three weeks post injury. Left knee controls were injected with 0.5ml normal saline. Cohorts of each group were euthanized at 2 and 6 months respectively. Histologic sections of the injury sites were evaluated for repair tissue quality using a modified grading scale. Six elements of repair were assessed and scored for the full thickness defect including: defect filling, integration of repair tissue, matrix staining, cellular morphology, surface architecture, and architecture of the reparative tissue. A maximum score of 22 points was possible, with higher scores representing poorer repair. Five elements of repair were assessed for the full thickness scratch defect including: the physical characteristic of the repair surface, the quality of the repair tissue, the presence of subsurface voids, the presence of cell death in the immediate periphery of the defect, and the presence of decreased matrix staining in the immediate periphery. A maximum score of 15 points was possible, with higher scores representing poorer repair. Cumulative scores for each category and group were compared utilizing one-way ANOVA and Kruskal-Wallis tests.

Results
Histological grading for full punch defects. Irrespective of the treatment or the timing of the injections groups, the full thickness punch defects universally demonstrated marked degeneration of the reparative tissue in all parameters measured. Defect filling was incomplete, and the repair tissue demonstrated poor matrix staining with multiple voids and severe surface fibrillation. The cellular morphology was disorganized with thin fibrocyte-like cells in the areas of cellular regeneration. Integration of the reparative tissue with the surrounding articular cartilage was poor in all cases. No statistically significant differences were noted between the hyaluronate treated knees and the saline-injected controls in any grading category. The timing of the injection sequence did not appear to have any effect on the outcome of the quality, quantity, or type of the repair tissue. The hyaluronate injections did not appear to offer protection to the bordering cartilage. Both the hyaluronate-treated cartilage and the saline-treated control cartilage demonstrated consistent cartilage cell death and decreased matrix staining in the regions bordering the cartilage defect.

Histological grading for full thickness scratch defects. The full thickness scratch defects demonstrated marked variability in the surface quality of the reparative tissue. Some specimens demonstrated a hypertrophic response, with the repair tissue extending beyond the surface margins. In all cases, this repair tissue was not well integrated with the surrounding uninjured cartilage, and demonstrated voids that extended to frank gap formation in some cases. Other samples maintained tissue abutment with only minimal subsurface voids. However, no statistically significant differences were noted in any of the assessment parameters between the hyaluronate-treated knees and the saline-treated controls. The hyaluronate injections did not appear to offer protection to the border cartilage. Both the hyaluronate-treated cartilage and the saline-treated control cartilage demonstrated cartilage cell death and decreased matrix staining in the regions bordering the cartilage defect.

Discussion
No significant differences were noted in the quantity or quality of the repair tissue at 2 or 6 months in either the scratch or the full thickness sections. Hyaluronic acid injections did not significantly alter the healing process or the natural degenerative process in this model of acute full thickness cartilage injuries. While the use of hyaluronate may hold promise for the treatment of chronic osteoarthritic changes, the efficacy in an acute cartilagenous injury appears to be doubtful.

References: